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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,856	01/07/2002	Susan Slaugenhaupt	1829-4004US1	5418

27123 7590 12/01/2004

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,856	SLAUGENHAUPT ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *8,9,15-28 and 36-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-14,29-35 and 43* is/are rejected.

7)☒ Claim(s) *2-7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/15/04;7/17/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-7, 10-14, 29-35 and 43 in the reply filed on August 16, 2004 is acknowledged. The traversal is on the ground(s) that there would not be any undue burden to examine the nucleic acids of Group I together with the proteins of Group II since the search would involve the same relevant patent and scientific literature. This is not found persuasive because However, it is maintained that undue burden would be required to examine the claims of Group II together with the claims of Group I as evidenced by the fact that the claims of Groups I and II have acquired a separate status in the art as recognized by their different classification and as recognized by their divergent subject matter. Further, a search of the subject matter of Group I is not co-extensive with a search of Group II. In particular, a search in the sequence databases for the genomic DNA and cDNA of SEQ ID NO: 1 and 2 is not co-extensive with a search for protein sequences of SEQ ID NO: 3 and a search in the NPL and patent literature for naturally occurring or isolated IKAP nucleic acids is not co-extensive with a search for naturally occurring or isolated IKAP proteins. Accordingly, undue burden would be required to examine the subject matter of Group II together with the subject matter of Group I.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

2. Claims 1-7, 10-14, 29-35 and 43 are objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR

§1.821(d). The claims should be amended to refer to the appropriate SEQ ID NO in place of the recited Figure.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14 and 29-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is indefinite over the recitation of "group comprising" because the claim recites an improper format for a Markush group. Claims which recite members of a Markush group must be "close-ended." This rejection may be overcome by amendment of the claim to recite "group consisting of". See MPEP 2173.05(h).

Claims 13 and 14 are indefinite because the claims are drawn to methods for producing wild-type and mutant IKAP proteins, respectively, yet each claim allows for the use of nucleic acids which encode both wild-type and mutant proteins. The nucleic acids of 10(b), (c), (d) and (f) are considered to encode for mutant proteins while the nucleic acids of 10(a) and (e) are considered to encode for wild-type proteins. Therefore, it is unclear as to how the nucleic acids of 10(b), (c), (d) and (f) can be used in the method of claim 13 to produce a wild-type protein and it is unclear as to how the nucleic acids of 10(a) and (e) can be used in the method of claim 14 to produce a mutant protein.

Claims 29-35 are indefinite over the recitation of "capable of detecting." Capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited oligonucleotides do in fact detect the FD1 or FD2 mutations or only have the potential to detect the FD1 or FD2 mutations, under some unspecified conditions or following some unstated modification of the oligonucleotides. Amendment of the claim to read e.g. "...oligonucleotide probe which detects" would obviate this rejection.

4. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for oligonucleotides which detect the FD1 or FD2 mutations in the IKBKAP gene, does not reasonably provide enablement for any oligonucleotide for detecting a mutation associated with FD wherein the oligonucleotide comprises a sequence which detects a FD mutation or comprises sequences which hybridize to a region flanking a FD mutation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claim 43 is drawn broadly to encompass oligonucleotides for detecting a mutation associated with FD wherein the oligonucleotide comprises a sequence which detects a FD mutation or comprises sequences which hybridize to a region flanking a FD mutation. The claim does not specify the sequence or length of the oligonucleotide, does not specify the gene to which the oligonucleotide hybridizes and does not specify the identity of the mutation. Accordingly, the claim encompasses oligonucleotides which detect any mutation in any gene which is associated with the occurrence of FD and oligonucleotides which hybridize to any sequence flanking a FD mutation, wherein the region may be located any distance from the FD mutation.

Nature of the Invention and State of the Art:

The specification teaches 2 mutations in the IKBKAP gene: a) the "FD1" mutation located at bp6 within intron 20, wherein a thymine is replaced by a cytosine; and b) the "FD2" located at position 2396 (bp73 of exon 19) wherein a guanine is replaced by a cytosine, leading to a missense arginine to proline mutation at amino acid position 696. The specification further teaches the complete cDNA sequence (SEQ ID NO: 7) and genomic sequence (SEQ ID NO: 6) of the IKBKAP gene. The IKBKAP genomic DNA spans 66,479 nucleotides. The specification and prior art do not teach any additional mutations in the IKBKAP gene and particularly does not teach any additional IKBKAP mutations associated with FD. Further, the prior art does not appear to teach any additional genes which are associated with FD or any additional mutations which are associated with FD.

The Relative Skill in the Art:

The level of skill in the art of molecular biology and diagnostics is relatively high.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying genes associated with a disease and detecting the presence of novel mutations associated with the occurrence of disease is highly unpredictable. Knowledge of the FD1 and FD2 mutations does not lead one to any additional mutations in the IKBKAP gene or any other gene. There is no common structural feature linking the broadly claimed oligonucleotides which are defined only in terms of their functional properties and not in terms of their structural properties. With respect to the IKBKAP gene, it is unpredictable as to which residues within this gene of over 60Kb are important to the functional activity of the encoded protein and which nucleotides are variable in nature and are associated with the occurrence of FD. To identify additional genes or mutations requires extensive, trial-by-error experimentation in which researchers may be required to map genes, perform linkage analysis to determine the inheritance pattern of polymorphisms, sequence genes, identify specific mutations in the sequenced gene, analyze members of the population which have FD and individuals who do not have FD for the presence or absence of a polymorphism or mutation and try to ascertain which specific polymorphisms or mutations are associated with the occurrence of disease. Such experimentation is considered to be undue.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably identify additional mutations in the IKBKAP gene or as to how to identify additional genes containing mutations associated with FD. While methods for sequencing genes

and comparing the sequence of genes from patients and control individuals are known in the art, such methods provide only the general guidelines that allow researchers to search for novel mutations. Providing methods for searching for a mutation and for additional FD-associated genes is not equivalent to teaching how to make and use specific oligonucleotides which detect specific FD mutations.

Working Examples:

Again, the specification teaches 2 mutations in the IKBKAP gene, namely the FD1 and FD2 mutations, as defined on page 3 of the specification. The specification does not provide any additional examples of FD-associated mutations in the IKBKAP gene or in other unspecified genes.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the claims do not bear a

reasonable correlation to the scope of enablement because the specification teaches only 2 members of the broadly claimed genus of oligonucleotides which detect any mutation in any gene associated with FD and oligonucleotides which hybridize to sequences at any distance to a region flanking a FD-associated mutation. As set forth above, in view of the unpredictability in the art, extensive experimentation would be required to identify additional IKBKAP mutations and mutations in other genes associated with FD. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art as to additional polymorphisms or mutations which are associated with FD and the lack of specific guidance provided by the specification, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Priority

5. Claims 1-5, 10-14, 29, 30, 34, 35 and 43 are entitled to the filing date of January 7, 2002. These claims are not entitled to priority to provisional application 60/260,080. Provisional application 60/260,080 provides a transmission letter stating that 56 sheets of drawings were filed. However, this application was not filed with a complete set of drawings. While Figure 6 states that the recited sequence is of a length of 66476 nucleotides, the drawing ends at nucleotide 53,050. Accordingly, the provisional application does not provide support for the presently claimed nucleic acids of SEQ ID NO: 1 (having a length of 66,476 nucleotides). It is noted that a claim as a whole is assigned an effective filing date (rather than the subject matter within a claim being assigned individual effective filing dates). Claims 1-5, 10-14, 29, 30, 34, 35 and 43

encompass the presently claimed full length sequence of SEQ ID NO: 1 and thereby these claims are not entitled to the priority of the provisional application.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Cohen (U.S. Patent No. 5,891,719).

Cohen teaches an isolated nucleic acid encoding for IKBKAP (referred to therein as 'IKAP; see SEQ ID NO: 1). The nucleic acid of Cohen contains a guanine at nucleotide position 2087, which corresponds to position 2397 of present SEQ ID NO: 2. It is a property of the nucleic acid of Cohen that it would be capable of detecting the FD mutation at position 2397. For example, use of the nucleic acid of Cohen in a SSCP assay would allow for the detection of a cytosine in place of a guanine at position 2397. Accordingly, the nucleic acid of Cohen anticipates the claimed invention.

7. Claim 43 is rejected under 35 U.S.C. 102(a) as being anticipated by Rubin (2002/0168656; cited in the IDS).

Rubin (page 1, column 2) discloses a cDNA encoding IKBKAP having GenBank Accession No. NM_003640. This cDNA is 4803 bp in length, whereas the IKBKAP cDNA of the present invention (Figure 7 and SEQ ID NO :2) is 5924bp in length. Rubin

further teaches mutations in the IKBKAP wherein the first mutation is a G to C transversion at nucleotide 2390 in exon 19 of Accession No. NM_003640 and the second mutation is a T to C transition in position 6 of the donor splice site for exon 6 (page 1, column 2). The reference also teaches primers for amplifying exons 19-21 (page 1, column 2 and page 2, column 1) and PCR amplification products containing each of the above mutations.. Accordingly, Rubin teaches oligonucleotides for detecting a mutation in FD, wherein the oligonucleotide hybridizes to a FD mutation or to a region flanking a FD mutation.

8. Claim 43 is rejected under 35 U.S.C. 102(a) as being anticipated by Anderson (American Journal of Human Genetics (March 2001) 68: 753-758; cited in the IDS).

Anderson (page 754) discloses a cDNA encoding human IKBKAP having GenBank Accession No. NM_003640. This cDNA is 4803 bp in length, whereas the IKBKAP cDNA of the present invention (Figure 7 and SEQ ID NO :2) is 5924bp in length. Anderson further teaches mutations in the IKBKAP wherein the first mutation is a G to C transversion at nucleotide 2390 in exon 19 of Accession No. NM_003640 and the second mutation is a T to C transition in position 6 of the donor splice site for exon 6 (page 754). The reference also teaches primers for amplifying exons 19-21 (Figures 1 and 4) and PCR amplification products containing each of the above mutations. Accordingly, Anderson teaches oligonucleotides for detecting a mutation in FD, wherein the oligonucleotide hybridizes to a FD mutation or to a region flanking a FD mutation.

9. Claims 1 and 43 is rejected under 35 U.S.C. 102(a) as being anticipated by Slaugenhaupt (American Journal of Human Genetics (March 2001) 68: 598-605; cited in the IDS).

Slaugenhaupt (page 600) discloses a 5.9 Kb cDNA encoding human IKBKAP having GenBank Accession No. AF153419. This cDNA is identical to the cDNA of present SEQ ID NO: 2 (i.e., Figure 7). Slaugenhaupt further teaches mutations in the IKBKAP wherein the first mutation is a G to C transversion at nucleotide 2397 in exon 19, resulting in a arginine to proline missense mutation at amino acid position 696 and the second mutation is a T to C transition in position 6 of the donor splice site for exon 6 (page 602). The reference also teaches amplification products containing the 2 mutations wherein the amplification products are generated by amplifying IKBKAP sequences using primers to exons 19 and 20/21 (page 599). Accordingly, Slaugenhaupt teaches oligonucleotides for detecting a mutation in FD, wherein the oligonucleotide hybridizes to a FD mutation.

10. Claims 1 and 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Gill et al (GenBank Accession No. AF153419, published 02 January 2001).

Gill discloses a 5.9 Kb cDNA encoding human IKBKAP having GenBank Accession No. AF153419. This cDNA is identical to the cDNA of present SEQ ID NO: 2 (i.e., Figure 7). The cDNA of Gill includes nucleotide position 2397 and hybridizes with IKBKAP nucleic acids comprising the 2397 FD mutation. Accordingly, Gill teaches an oligonucleotide for detecting a mutation in FD, wherein the oligonucleotide hybridizes to a FD mutation.

11. Claims 1 and 43 is rejected under 35 U.S.C. 102(a) as being anticipated by Slaugenhaupt et al (GenBank Accession No. AF153419, published 28 February 2001; cited in the IDS).

Slaugenhaupt discloses a 5.9 Kb cDNA encoding human IKBKAP having GenBank Accession No. AF153419. This cDNA is identical to the cDNA of present SEQ ID NO: 2 (i.e., Figure 7). In the comments section of the sequence, it is noted that a polymorphism is present at nucleotide position 2397. The cDNA of Slaugenhaupt includes nucleotide position 2397 and hybridizes with IKBKAP nucleic acids comprising the 2397 FD mutation. Accordingly, Slaugenhaupt teaches an oligonucleotide for detecting a mutation in FD, wherein the oligonucleotide hybridizes to a FD mutation.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29, 30, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen in view of Fodor (U.S. Patent NO. 5,968,740).

Cohen teaches an isolated nucleic acid encoding for IKBKAP (referred to therein as 'IKAP'; see SEQ ID NO: 1). The nucleic acid of Cohen contains a guanine at nucleotide position 2087, which corresponds to position 2397 of present SEQ ID NO: 2. It is a property of the nucleic acid of Cohen that it would be capable of detecting the FD mutation at position 2397. For example, use of the nucleic acid of Cohen in a SSCP assay would allow for the detection of a cytosine in place of a guanine at position 2397. Additionally, Cohen teaches detecting IKBKAP nucleic acids by first amplifying the nucleic acids by PCR and then detecting the amplified nucleic acids using hybridization probes (columns 5 and 6). Cohen also exemplifies nucleic acids useful as primers or probes (see, e.g., Table 3). Cohen does not teach packaging the primers and probes in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Fodor (column 3) discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits may include any of the reagents necessary for performing methods for detecting a target nucleic acid. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the IKBKAP nucleic acids of Cohen, including

primers for amplifying IKBKAP and probes for detecting IKBKAP, in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art.

With respect to claims 34 and 35, Cohen does not teach further including oligonucleotides for detecting additional wildtype or mutant genes in a kit. However, Fodor (e.g., column 10) teaches arrays of probes which can be used to simultaneously detect distinct target nucleic acids, wherein the target nucleic acids may be either wildtype sequences or mutant sequences. The reference teaches that such arrays are useful for diagnosing a variety of diseases, including cystic fibrosis and teaches that the array may contain hundreds to thousands of probes (see column 19). Additionally, Fodor teaches kits containing arrays of nucleic acid probes (column 3). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, such as probes to the cystic fibrosis gene, in the kit containing probes and/or primers to the IKBKAP gene in order to have generated kits that could be used to simultaneously detect the presence of wildtype and/or mutant IKBKAP sequences and other diseases associated diseases.

13. Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slaugenhaupt (American Journal of Human Genetics (March 2001) 68: 598-605; cited in the IDS) in view of Cohen.

Slaugenhaupt (page 600) discloses a 5.9 Kb cDNA encoding human IKBKAP having GenBank Accession No. AF153419. This cDNA is identical to the cDNA of present SEQ ID NO: 2 (i.e., Figure 7). Slaugenhaupt further teaches mutations in the IKBKAP wherein the first mutation is a G to C transversion at nucleotide 2397 in exon

19, resulting in a arginine to proline missense mutation at amino acid position 696 and the second mutation is a T to C transition in position 6 of the donor splice site for exon 6 (page 602). The reference also teaches amplification products containing the 2 mutations wherein the amplification products are generated by amplifying IKBKAP sequences using primers to exons 19 and 20/21 (page 599). Slaugenhaupt does not specifically teach vectors and host cells comprising the IKBKAP cDNA or methods for producing IKBKAP wildtype or mutant proteins using host cells transformed with vectors containing IKBKAP cDNAs.

However, Cohen teaches an isolated nucleic acid encoding for IKBKAP (referred to therein as 'IKAP'; see SEQ ID NO: 1). Cohen (e.g., column 3) further teaches vectors and host cells comprising the IKBKAP cDNA. The reference (column 3 and 4) teaches methods for synthesizing recombinant IKBKAP using host cells transformed with IKBKAP, wherein the host cells are preferably human or other mammalian cells. Cohen (column 7-8) teaches use of the recombinant protein to identify compounds that bind to IKBKAP, which can then potentially be used for diagnostic and therapeutic applications.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have cloned the cDNAs of Slaugenhaupt into vectors, to have transformed host cells with the recombinant vectors and to have used the resulting transformed host cells to synthesize IKBKAP proteins in order to have provided recombinant IKBKAP wildtype and mutant proteins that could be used to further study the properties of these proteins and could be used in assays to identify potential diagnostic and therapeutic agents which bind IKBKAP proteins.

14. Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gill et al (GenBank Accession No. AF153419, published 02 January 2001) in view of Cohen.

Gill discloses a 5.9 Kb cDNA encoding human IKBKAP having GenBank Accession No. AF153419. This cDNA is identical to the cDNA of present SEQ ID NO: 2 (i.e., Figure 7). The cDNA of Gill includes nucleotide position 2397 and hybridizes with IKBKAP nucleic acids comprising the 2397 FD mutation. Gill does not specifically teach vectors and host cells comprising the IKBKAP cDNA or methods for producing IKBKAP wildtype or mutant proteins using host cells transformed with vectors containing IKBKAP cDNAs.

However, Cohen teaches an isolated nucleic acid encoding for IKBKAP (referred to therein as 'IKAP'; see SEQ ID NO: 1). Cohen (e.g., column 3) further teaches vectors and host cells comprising the IKBKAP cDNA. The reference (column 3 and 4) teaches methods for synthesizing recombinant IKBKAP using host cells transformed with IKBKAP, wherein the host cells are preferably human or other mammalian cells. Cohen (column 7-8) teaches use of the recombinant protein to identify compounds that bind to IKBKAP, which can then potentially be used for diagnostic and therapeutic applications.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have cloned the cDNAs of Gill into vectors, to have transformed host cells with the recombinant vectors and to have used the resulting transformed host cells to synthesize IKBKAP proteins in order to have provided

recombinant IKBKAP wildtype and mutant proteins that could be used to further study the properties of these proteins and could be used in assays to identify potential diagnostic and therapeutic agents which bind IKBKAP proteins. With respect to claim 14, it is noted that this claim has been interpreted as including methods which synthesize proteins using the cDNA of present SEQ ID NO: 1, since the claim recites transforming host cells with a vector containing a cDNA of present claim 1 and present claim 1 includes the cDNA of SEQ ID NO: 1 (see 1(e)).

15. Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slaugenhaupt et al (GenBank Accession No. AF153419, published 28 February 2001; cited in the IDS) in view of Cohen.

Slaugenhaupt discloses a 5.9 Kb cDNA encoding human IKBKAP having GenBank Accession No. AF153419. This cDNA is identical to the cDNA of present SEQ ID NO: 2 (i.e., Figure 7). In the comments section of the sequence, it is noted that a polymorphism is present at nucleotide position 2397. The cDNA of Slaugenhaupt includes nucleotide position 2397 and hybridizes with IKBKAP nucleic acids comprising the 2397 FD mutation. Slaugenhaupt does not specifically teach vectors and host cells comprising the IKBKAP cDNA or methods for producing IKBKAP wildtype or mutant proteins using host cells transformed with vectors containing IKBKAP cDNAs.

However, Cohen teaches an isolated nucleic acid encoding for IKBKAP (referred to therein as 'IKAP'; see SEQ ID NO: 1). Cohen (e.g., column 3) further teaches vectors and host cells comprising the IKBKAP cDNA. The reference (column 3 and 4) teaches methods for synthesizing recombinant IKBKAP using host cells transformed with

IKBKAP, wherein the host cells are preferably human or other mammalian cells. Cohen (column 7-8) teaches use of the recombinant protein to identify compounds that bind to IKBKAP, which can then potentially be used for diagnostic and therapeutic applications.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have cloned the cDNAs of Slaugenhaupt into vectors, to have transformed host cells with the recombinant vectors and to have used the resulting transformed host cells to synthesize IKBKAP proteins in order to have provided recombinant IKBKAP wildtype and mutant proteins that could be used to further study the properties of these proteins and could be used in assays to identify potential diagnostic and therapeutic agents which bind IKBKAP proteins. With respect to claim 14, it is noted that this claim has been interpreted as including methods which synthesize proteins using the cDNA of present SEQ ID NO: 1, since the claim recites transforming host cells with a vector containing a cDNA of present claim 1 and present claim 1 includes the cDNA of SEQ ID NO: 1 (see 1(e)).

16. Claims 29, 30, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubin in view of Fodor (U.S. Patent NO. 5,968,740).

Rubin (page 1, column 2) discloses a cDNA encoding IKBKAP having GenBank Accession No. NM_003640. This cDNA is 4803 bp in length, whereas the IKBKAP cDNA of the present invention (Figure 7 and SEQ ID NO :2) is 5924bp in length. Rubin further teaches mutations in the IKBKAP wherein the first mutation is a G to C transversion at nucleotide 2390 in exon 19 of Accession No. NM_003640 and the second mutation is a T to C transition in position 6 of the donor splice site for exon 6

(page 1, column 2). The reference also teaches primers for amplifying exons 19-21 (page 1, column 2 and page 2, column 1) and PCR amplification products containing each of the above mutations. Accordingly, Rubin teaches oligonucleotides for detecting a mutation in FD, wherein the oligonucleotide hybridizes to a FD mutation or to a region flanking a FD mutation. Rubin does not teach packaging the IKBKAP oligonucleotides in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Fodor (column 3) discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits may include any of the reagents necessary for performing methods for detecting a target nucleic acid. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the IKBKAP nucleic acids of IKBKAP, including primers for amplifying IKBKAP and probes for detecting IKBKAP, in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art.

With respect to claims 34 and 35, Rubin does not teach further including oligonucleotides for detecting additional wildtype or mutant genes in a kit. However, Fodor (e.g., column 10) teaches arrays of probes which can be used to simultaneously detect distinct target nucleic acids, wherein the target nucleic acids may be either wildtype sequences or mutant sequences. The reference teaches that such arrays are useful for diagnosing a variety of diseases, including cystic fibrosis and teaches that the array may contain hundreds to thousands of probes (see column 19). Additionally,

Fodor teaches kits containing arrays of nucleic acid probes (column 3). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, such as probes to the cystic fibrosis gene, in the kit containing probes and/or primers to the IKBKAP gene in order to have generated kits that could be used to simultaneously detect the presence of wildtype and/or mutant IKBKAP sequences and other diseases associated diseases.

17. Claims 29, 30, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Fodor (U.S. Patent NO. 5,968,740).

Anderson (page 754) discloses a cDNA encoding human IKBKAP having GenBank Accession No. NM_003640. This cDNA is 4803 bp in length, whereas the IKBKAP cDNA of the present invention (Figure 7 and SEQ ID NO :2) is 5924bp in length. Anderson further teaches mutations in the IKBKAP wherein the first mutation is a G to C transversion at nucleotide 2390 in exon 19 of Accession No. NM_003640 and the second mutation is a T to C transition in position 6 of the donor splice site for exon 6 (page 754). The reference also teaches primers for amplifying exons 19-21 (Figures 1 and 4) and PCR amplification products containing each of the above mutations. Accordingly, Anderson teaches oligonucleotides for detecting a mutation in FD, wherein the oligonucleotide hybridizes to a FD mutation or to a region flanking a FD mutation.

Anderson does not teach packaging the IKBKAP oligonucleotides in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Fodor (column 3) discloses the general concept of kits for performing nucleic acid

hybridization methods and discloses that kits may include any of the reagents necessary for performing methods for detecting a target nucleic acid. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the IKBKAP nucleic acids of IKBKAP, including primers for amplifying IKBKAP and probes for detecting IKBKAP, in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art.

With respect to claims 34 and 35, Anderson does not teach further including oligonucleotides for detecting additional wildtype or mutant genes in a kit. However, Fodor (e.g., column 10) teaches arrays of probes which can be used to simultaneously detect distinct target nucleic acids, wherein the target nucleic acids may be either wildtype sequences or mutant sequences. The reference teaches that such arrays are useful for diagnosing a variety of diseases, including cystic fibrosis and teaches that the array may contain hundreds to thousands of probes (see column 19). Additionally, Fodor teaches kits containing arrays of nucleic acid probes (column 3). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, such as probes to the cystic fibrosis gene, in the kit containing probes and/or primers to the IKBKAP gene in order to have generated kits that could be used to simultaneously detect the presence of wildtype and/or mutant IKBKAP sequences and other diseases associated diseases.

18. Claims 29, 30, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slaugenhaupt (American Journal of Human Genetics (March 2001) 68: 598-605; cited in the IDS) in view of Fodor (U.S. Patent NO. 5,968,740).

Slaugenhaupt (page 600) discloses a 5.9 Kb cDNA encoding human IKBKAP having GenBank Accession No. AF153419. This cDNA is identical to the cDNA of present SEQ ID NO: 2 (i.e., Figure 7). Slaugenhaupt further teaches mutations in the IKBKAP wherein the first mutation is a G to C transversion at nucleotide 2397 in exon 19, resulting in a arginine to proline missense mutation at amino acid position 696 and the second mutation is a T to C transition in position 6 of the donor splice site for exon 6 (page 602). The reference also teaches amplification products containing the 2 mutations wherein the amplification products are generated by amplifying IKBKAP sequences using primers to exons 19 and 20/21 (page 599). Accordingly, Slaugenhaupt teaches oligonucleotides for detecting a mutation in FD, wherein the oligonucleotide hybridizes to a FD mutation. Slaugenhaupt does not teach packaging the IKBKAP oligonucleotides in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Fodor (column 3) discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits may include any of the reagents necessary for performing methods for detecting a target nucleic acid. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the IKBKAP nucleic acids of IKBKAP, including primers for amplifying IKBKAP and probes for detecting IKBKAP, in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art.

With respect to claims 34 and 35, Slaughenpaut does not teach further including oligonucleotides for detecting additional wildtype or mutant genes in a kit. However, Fodor (e.g., column 10) teaches arrays of probes which can be used to simultaneously detect distinct target nucleic acids, wherein the target nucleic acids may be either wildtype sequences or mutant sequences. The reference teaches that such arrays are useful for diagnosing a variety of diseases, including cystic fibrosis and teaches that the array may contain hundreds to thousands of probes (see column 19). Additionally, Fodor teaches kits containing arrays of nucleic acid probes (column 3). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, such as probes to the cystic fibrosis gene, in the kit containing probes and/or primers to the IKBKAP gene in order to have generated kits that could be used to simultaneously detect the presence of wildtype and/or mutant IKBKAP sequences and other diseases associated diseases.

19. Claims 29, 30, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gill in view of Cohen and further in view of Fodor (U.S. Patent NO. 5,968,740).

The teachings of Gill and Cohen are presented above. The combined references teach a IKBKAP cDNA of 5.9 Kb identical to the cDNA of present SEQ ID NO: 1. The combined references also teach detecting IKBKAP nucleic acids using oligonucleotide probes and primers. The combined references not teach packaging the IKBKAP oligonucleotides in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Fodor (column 3) discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits may include any of the reagents necessary for performing methods for detecting a target nucleic acid. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the IKBKAP nucleic acids of IKBKAP, including primers for amplifying IKBKAP and probes for detecting IKBKAP, in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art.

With respect to claims 34 and 35, Gill and Cohen do not teach further including oligonucleotides for detecting additional wildtype or mutant genes in a kit. However, Fodor (e.g., column 10) teaches arrays of probes which can be used to simultaneously detect distinct target nucleic acids, wherein the target nucleic acids may be either wildtype sequences or mutant sequences. The reference teaches that such arrays are useful for diagnosing a variety of diseases, including cystic fibrosis and teaches that the array may contain hundreds to thousands of probes (see column 19). Additionally, Fodor teaches kits containing arrays of nucleic acid probes (column 3). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, such as probes to the cystic fibrosis gene, in the kit containing probes and/or primers to the IKBKAP gene in order to have generated kits that could be used to simultaneously detect the presence of wildtype and/or mutant IKBKAP sequences and other diseases associated diseases.

20. Claims 29, 30, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slaugenhaupt et al (GenBank Accession No. AF153419, published 28 February 2001; cited in the IDS) in view of Cohen and further in view of Fodor (U.S. Patent NO. 5,968,740).

The teachings of Slaugenhaupt and Cohen are presented above. The combined references teach a IKBKAP cDNA of 5.9 Kb identical to the cDNA of present SEQ ID NO: 1. The combined references also teach detecting IKBKAP nucleic acids using oligonucleotide probes and primers. The combined references not teach packaging the IKBKAP oligonucleotides in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Fodor (column 3) discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits may include any of the reagents necessary for performing methods for detecting a target nucleic acid. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the IKBKAP nucleic acids of IKBKAP, including primers for amplifying IKBKAP and probes for detecting IKBKAP, in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art.

With respect to claims 34 and 35 Slaugenhaupt and Cohen do not teach further including oligonucleotides for detecting additional wildtype or mutant genes in a kit. However, Fodor (e.g., column 10) teaches arrays of probes which can be used to simultaneously detect distinct target nucleic acids, wherein the target nucleic acids may

be either wildtype sequences or mutant sequences. The reference teaches that such arrays are useful for diagnosing a variety of diseases, including cystic fibrosis and teaches that the array may contain hundreds to thousands of probes (see column 19). Additionally, Fodor teaches kits containing arrays of nucleic acid probes (column 3). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, such as probes to the cystic fibrosis gene, in the kit containing probes and/or primers to the IKBKAP gene in order to have generated kits that could be used to simultaneously detect the presence of wildtype and/or mutant IKBKAP sequences and other diseases associated diseases.

21. If a copy of a provisional application listed on the bottom portion of the accompanying Notice of References Cited (PTO-892) form is not included with this Office action and the PTO-892 has been annotated to indicate that the copy was not readily available, it is because the copy could not be readily obtained when the Office action was mailed. Should applicant desire a copy of such a provisional application, applicant should promptly request the copy from the Office of Public Records (OPR) in accordance with 37 CFR 1.14(a)(1)(iv), paying the required fee under 37 CFR 1.19(b)(1). If a copy is ordered from OPR, the shortened statutory period for reply to this Office action will not be reset under MPEP § 710.06 unless applicant can demonstrate a substantial delay by the Office in fulfilling the order for the copy of the provisional application. Where the applicant has been notified on the PTO-892 that a copy of the provisional application is not readily available, the provision of MPEP

§ 707.05(a) that a copy of the cited reference will be automatically furnished without charge does not apply.

22. Claims 2-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Carla Myers
October 27, 2004